

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of Products Related to Vitamin A. VIII. The Synthesis of 1-(Cyclohexen-1'-yl)-3-methyl-3-epoxybutyne-1 and Related Products¹

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The availability of a reliable method for the synthesis of biologically active vitamin A products⁴ made it desirable to investigate the effect of various substituents in the cyclohexene ring on the biological activity of the final products. For example, one could synthesize a vitamin A analog without any substituents in the cyclohexene ring, or even substitute a benzene ring for the latter. In order to effect these changes, several new key intermediates have been synthesized and are herein reported.

In the synthesis of the epoxides (VI) and (VII) four different series were studied. In the first series cyclohexanone was acetylenated in liquid ammonia with sodium acetylide and the 1-ethynylcyclohexanol-1 (II, R₁ = R₂ = R₃ = H) formed dehydrated at 290–300° using aluminum phosphate as the dehydrating catalyst. This dehydration has been previously studied using alumina⁵ and aluminum sulfate⁶ catalysts but no analytical data beyond a series of widely different physical constants have been reported. The same holds true with the results of other investigators who prepared this enyne by other procedures.^{7,8} The lack of chemical evidence for the existence of the pure enyne is perhaps significant, since even in our case all low boiling fractions were found to possess values for active hydrogen ranging from less than 0.1 to 0.9, in spite of the fact that hydrogenation values and other properties were almost identical to those of the pure enyne.

In the second series, 2-methyl-1-ethynylcyclohexanol-1 was prepared in liquid ammonia from 2-methylcyclohexanone and sodium acetylide. When this ethynylcyclohexanol was allowed to stand at 0° for sixteen hours, it separated into two forms: a solid and a liquid form of approximately equal weight. Since the addition of acetylene to the carbonyl group of the 2-methylcyclohexanone introduces a second asymmetric carbon atom, one would expect two pairs of enantiomorphs, a fact which has been overlooked by earlier investiga-

tors^{9,10} although Wang and Hu¹¹ reported both the solid and the liquid forms. Dehydration of both the liquid and the solid forms over aluminum phosphate at 290–295° produced the same ethynylcyclohexene in yields of 52 and 27%, respectively. Ozonization of the enyne, produced from either the solid or the liquid form, yielded the same keto acid, namely, 6-ketoheptoic acid. The 2,4-dinitrophenylhydrazone of this acid from either ozonization product had the same m. p., and mixed m. p. showed no depression. Furthermore, the semicarbazone of the keto-acid from either ozonization product had essentially the same m. p. which was identical with the m. p. of the semicarbazone of 6-ketoheptoic acid reported by Wallach.¹² Therefore, we are forced to conclude that both enynes must have essentially the same structure.

That the solid carbinol presumably corresponds to the *cis* form and the liquid to the *trans* form may be deduced from the tendency of each to dehydrate. It is well known¹³ that *trans* elimination of water or halogen acids proceeds more smoothly than the corresponding *cis* elimination, and the low yields of the enyne obtained from the solid carbinol are in accord with these facts.

In the third series 2,6,6-trimethyl-1-ethynylcyclohexanol-1 was prepared in liquid ammonia from 2,6,6-trimethylcyclohexanone and sodium acetylide. Although two pairs of enantiomorphs were also expected in this case, only one product was obtained and attempts to separate it into two forms were not successful. The dehydration of this acetylene carbinol to produce the corresponding enyne in good yields was difficult to accomplish.¹⁴ Methods which were known to yield good results with other acetylene carbinols were either too drastic or too ineffective in producing the proper dehydration. Small yields of the desired enyne were obtained when the acetylene carbinol was dehydrated at 270–290° using aluminum phosphate on pumice as catalyst or when heated with either succinic anhydride in dibutyl phthalate or with a mixture of succinic anhydride and small amounts of glacial metaphosphoric acid. Perhaps

(1) Paper No. VII, "Vitamins and Hormones," **5**, 1 (1947), Academic Press, Inc., New York, N. Y.

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(4) (a) Milas, U. S. Patents, 2,369,156–2,369,168 inclusive, Feb. 13 (1945); 2,382,085–2,382,086, Aug. 14 (1945); *Science*, **103**, 581 (1946); (b) Milas, *et al.*, *THIS JOURNAL*, **70**, 1597 (1948); (c) Isler, Kofler, Huber and Ronco, *Experientia*, **2**, 31 (1946); Jubilee Volume to Emil C. Borell, Hoffman-LaRoche and Co., Basle, 1946, p. 31.

(5) Friedr. Farbenfab. von Baeyer and Co., German Patent 290,558; *Chem. Zentr.*, **87**, I, 644 (1916).

(6) Carothers and Coffman, *THIS JOURNAL*, **54**, 4071 (1932).

(7) Mousseron, *Compt. rend.*, **217**, 155 (1943).

(8) Azerbaev, *J. Gen. Chem. (U. S. S. R.)*, **15**, 412 (1945).

(9) Cook and Lawrence, *J. Chem. Soc.*, 58 (1938).

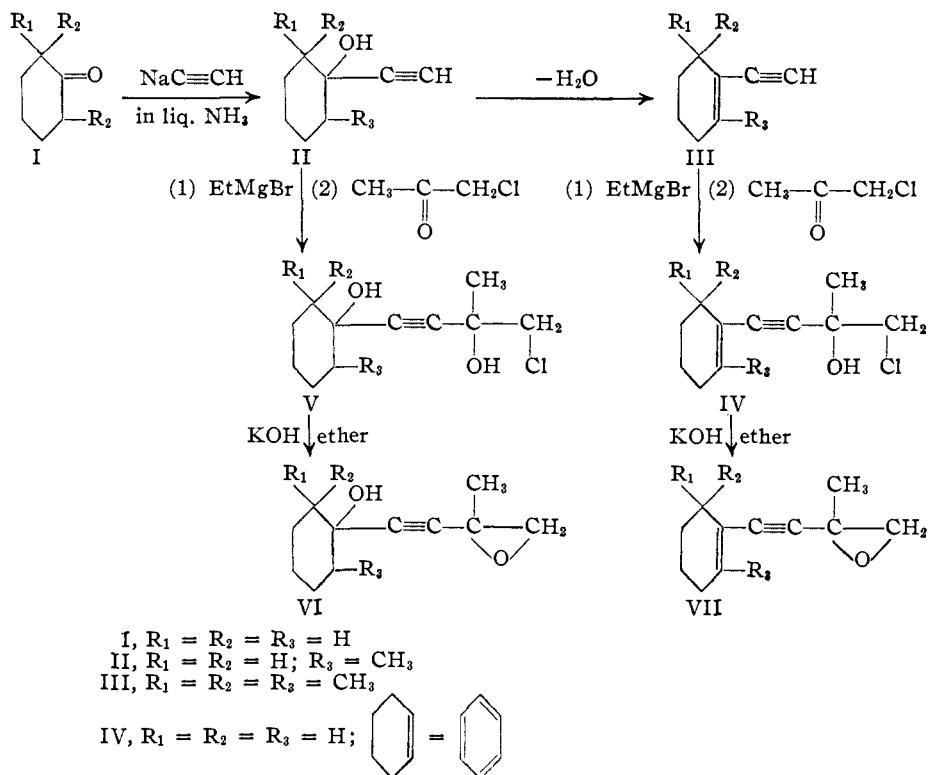
(10) Marvel, Mazingo and White, *THIS JOURNAL*, **62**, 1880 (1940).

(11) Wang and Hu, *J. Chinese Chem. Soc.*, **10**, 1 (1943).

(12) Wallach [*Ann.*, **329**, 376 (1903)] reports the m. p. of the semicarbazone of 6-ketoheptoic acid as 144–145°.

(13) (a) Michael, *J. prakt. Chem.*, **46**, 210 (1892); (b) Bartlett and Rosenwald, *THIS JOURNAL*, **56**, 1990 (1934); (c) Winstein, Pressman and Young, *ibid.*, **61**, 1645 (1939); (d) Huckel, Tappe and Legutke, *Ann.*, **543**, 191 (1940).

(14) Since this enyne is an important intermediate in the synthesis of vitamin A itself, work is being continued to study the mechanism of its formation.



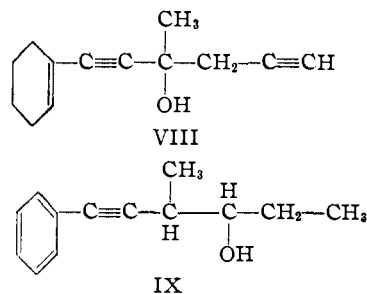
the reason for our difficulty in obtaining good yields of the enyne in this case is due to the possibility of the hydroxyl group being hindered by the methyl groups. A similar case has been reported recently¹⁵ with 1-(2,4-dimethylphenyl)-2,6-dimethylcyclohexanol which could not be dehydrated with potassium acid sulfate at 190–200°, or with boiling acetic anhydride. However, when it was refluxed with anhydrous oxalic acid at 200–220°, a yield of 81% of the corresponding cyclohexene derivative was obtained.¹⁶ When this method was applied to our acetylene carbinol only small amounts (3%) of the pure enyne were obtained.

In the subsequent step of the synthesis of the epoxides either the enynes (III) or the carbinols (II) were allowed to react via their Grignard reagents with chloroacetone to form the corresponding chlorohydrins (V or VI).¹⁷ In this step phenylacetylene was added to the list to afford comparison of the benzene ring with the cyclohexene ring.

Dehydrochlorination of the chlorohydrins was effected with powdered potassium hydroxide in quantities two to three times that of the theoretical. Sodamide was found equally effective, but an organic base such as triethylamine was completely ineffective. All the epoxides prepared

in this investigation responded slowly to the fuchsin-aldehyde test, and in acid solution they yielded crystalline 2,4-dinitrophenylhydrazones.

In the vitamin A synthesis cited in the early part of this paper, 1-[2',6',6'-trimethylcyclohexen-1'-yl]-3-methylbuten-1-yl-4 was the key intermediate. This was either acetylenated in liquid ammonia or allowed to react with a Grignard of an ethynyl compound of the proper structure. Both of these reactions were tested with some of our epoxides. For example, when 1-(cyclohexen-1'-yl)-3-methyl-3-epoxybutyne-1 was allowed to react in liquid ammonia with lithium acetylide, 1-(cyclohexen-1'-yl)-3-methyl-3-hydroxy hexadiyne-1,5 (VIII) was formed. Similarly, when 1-phenyl-3-methyl-3-epoxybutyne-1 was treated with ethylmagnesium bromide the carbinol (IX) was presumably formed, since it is well known¹⁸



(15) Carlin, *THIS JOURNAL*, **67**, 928 (1945).

(16) Carlin and Constantine, *ibid.*, **69**, 50 (1947).

(17) (a) Lespieau, *Compt. rend.*, **180**, 442, 557 (1925); *Bull. soc. chim.*, **43**, 199, 657 (1928); (b) Favorsky and Tikhomolov, *Compt. rend.*, **208**, 728 (1936); *J. Gen. Chem. (U. S. S. R.)*, **10**, 1501 (1940); (c) Herschstein, *ibid.*, **12**, 132 (1942).

(18) (a) Fourneau and Tiffeneau, *Bull. soc. chim.*, **33**, 741 (1905); *Compt. rend.*, **145**, 437 (1907); (b) Henry, *Bull. acad. roy. Belg.*, **162** (1907); *Compt. rend.*, **145**, 21 (1907); (c) Hess, *Ber.*, **46**, 3117 (1913).

that a Grignard reagent reacts with an unsymmetrically substituted epoxide to form secondary rather than tertiary alcohols. The structure of (VIII) and (IX) are only provisionally proposed and further work is being done to establish the structure of this type of compounds.

It is therefore seen that the success of the synthesis of vitamin A itself or its analogs, in which the methyl groups of the cyclohexene ring may be changed or left out entirely, can be achieved by by-passing β -ionone.

Experimental

1-Ethynylcyclohexanol-1.—Five hundred grams of pure cyclohexanone was added dropwise with stirring to a mixture of sodium acetylide (from 117 g. of sodium) and liquid ammonia (3 l.) at -50° in the course of three hours. Stirring was continued overnight while a slow stream of dry acetylene was allowed to pass through the solution. The ammonia was then allowed to evaporate and the residue acidified with 200 g. of tartaric acid in 500 cc. of water and extracted with ether. After the ether solution was dried and the ether removed, the residue was fractionated through a four-foot packed column and the fraction (518 g., 82%) boiling at $74-77^\circ$ (15 mm.) or $79-81^\circ$ (21 mm.) collected and analyzed. The supercooled liquid had an n_D^{20} 1.4823. On standing the liquid solidified completely; m. p. $31-32^\circ$. Marvel, *et al.*,¹⁹ gave a m. p. of $31-32^\circ$.

Anal. Calcd. for $C_8H_{12}O$: active hydrogen, 2.00. Found: A. H. (Zerewitinoff), 1.97, 2.02.

2-Methyl-1-ethynylcyclohexanol-1.—This acetylene carbinol was prepared in exactly the same way as the previous one in liquid ammonia from 560 g. of 2-methylcyclohexanone (b. p. $160.5-161^\circ$, n_D^{20} 1.4465) and sodium acetylide (from 130 g. of sodium). The product was fractionated through a four-foot packed column and the fraction (464 g., 67%) boiling at $98-105^\circ$ (45 mm.) collected and allowed to stand at 0° for sixteen hours, whereby it separated into two fractions: a solid fraction (227 g.) and a liquid portion (225 g.). The solid was recrystallized from petroleum ether, m. p. $61.0-61.5^\circ$ (cor.). The liquid portion was redistilled; b. p. 84° (17 mm.). Further attempts to obtain crystals from the liquid portion were unsuccessful. Wang and Hu²⁰ gave 60 and 85° (18 mm.), respectively.

Anal. Calcd. for $C_9H_{14}O$: A. H., 2.00. Found (crystalline): A. H. (Zerewitinoff), 2.0, 1.97. Found (liquid): A. H. (Zerewitinoff), 2.0, 2.0.

2,6,6-Trimethyl-1-ethynylcyclohexanol-1.—In a similar manner this acetylene carbinol was prepared in liquid ammonia from 560 g. of 2,6,6-trimethylcyclohexanone [b. p. $177-178.5^\circ$ (758 mm.), or $69-71.5^\circ$ (20 mm.); n_D^{20} 1.4465]²¹ and sodium acetylide (from 92 g. of sodium). The final product was fractionated through a four-foot packed column and the fraction (524 g., 79%) boiling at $212-212.4^\circ$ (760 mm.) or $88-90^\circ$ (20 mm.) collected and analyzed; n_D^{25} 1.4740; d_4^{25} 0.9300; *MRD* (calcd.), 50.32; *MRD* (obsd.), 50.25.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; unsaturation, 2.0 $\overline{\overline{}}$; A. H. (Zerewitinoff), 2.0. Found: C, 79.51, 79.45, 79.31; H, 10.86, 11.23, 11.21; unsaturation, 2.11 (Pt), 2.02 (Pd) $\overline{\overline{}}$; A. H. (Zerewitinoff), 2.0, 2.04.

1-Ethynylcyclohexene-1.—1-Ethynylcyclohexanol-1 was dehydrated by passing it upwards at the rate of 75 g. per hour under a slightly reduced pressure (175-180 mm.) through a glass tube 2.5×24 cm. packed with a 5:1 mixture of pumice and aluminum phosphate and main-

tained at a temperature of $290-300^\circ$. The vapors were condensed and fractionated through a four-foot packed column and the fraction (52% per pass) boiling at 47° (13 mm.) was collected and analyzed. Although this product showed the correct hydrogenation value, its Zerewitinoff value was between 0.6 and 0.8. It was therefore purified further via its silver derivative which was decomposed either with hydrogen sulfide or ammonium thiocyanate and the pure enyne recovered. For example, from 9 g. of crude 1-ethynylcyclohexene-1 6 g. of pure enyne was obtained boiling at $52-53^\circ$ (30 mm.) or $63-64^\circ$ (52 mm.) or $137-138^\circ$ (760 mm.); n_D^{25} 1.4934; d_4^{25} 0.8843; *MRD* (calcd.), 34.48; *MRD* (obsd.), 34.90. It also showed a maximum in the ultraviolet at 224μ , $\log \epsilon_{mol}$ 4.13.

Anal. Calcd. for C_8H_{10} : C, 90.50; H, 9.50; unsaturation, 3.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 90.44; H, 9.52; unsaturation, 3.19 $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.01, 1.0, 1.03.

2-Methyl-1-ethynylcyclohexene-1.—(a) From liquid 2-methyl-1-ethynylcyclohexanol-1. When 250 g. of this ethynylcarbinol was dehydrated under the same conditions as in the previous case and the crude product fractionated, a fraction (103 g., 47% per pass) was obtained which boiled at 55° (20 mm.) and had a Zerewitinoff value of 0.9. This was further purified through its silver derivative and the recovered enyne had a b. p. of $63-65^\circ$ (30 mm.) and gave correct analytical values; n_D^{25} 1.4895; d_4^{25} 0.8827; *MRD* (calcd.), 39.09; *MRD* (obsd.), 39.41. It also showed a maximum in the ultraviolet at 229μ , $\log \epsilon_{mol}$ 4.0.

Anal. Calcd. for C_9H_{12} : C, 89.93; H, 10.07; A. H., 1.0. Found: C, 89.71; H, 10.16; A. H. (Zerewitinoff), 1.0, 0.97.

(b) From solid 2-methyl-1-ethynylcyclohexanol-1: From 180 g. of solid 2-methyl-1-ethynylcyclohexanol-1, 84 g. of an enyne was obtained which had a b. p. of 57° (30 mm.) and a Zerewitinoff value of 0.5. This corresponds to a 27% yield per pass. This crude enyne was purified through its silver derivative and the pure product had a b. p. of $63.5-64^\circ$ (30 mm.) and gave correct analytical values; n_D^{25} 1.4883; d_4^{25} 0.8820; *MRD* (calcd.), 39.09; *MRD* (obsd.), 39.26. It also showed a maximum in the ultraviolet at 229μ , $\log \epsilon_{mol}$ 4.06.

Anal. Calcd. for C_9H_{12} : C, 89.93; H, 10.07; A. H., 1.0. Found: C, 89.75; H, 10.20; A. H. (Zerewitinoff), 1.0.

Ozonization of the Two 2-Methyl-1-ethynylcyclohexenes.—Using the method developed by Strain,²² 2 g. of each enyne was ozonized and the 2,4-dinitrophenylhydrazones precipitated and recrystallized from aqueous acetic acid solution.

From the enyne obtained by the dehydration of the solid 2-methyl-1-ethynylcyclohexanol-1, a pure 2,4-dinitrophenylhydrazone was obtained, m. p. $132.6-133.1^\circ$ (cor.).

Anal. Calcd. for $C_{13}H_{16}O_6N_4$: C, 48.14; H, 4.97; N, 17.28; neut. equiv., 324. Found: C, 47.97; H, 4.89; N, 16.96; neut. equiv., 327.

From the enyne obtained from the liquid 2-methyl-1-ethynylcyclohexanol-1, the pure 2,4-dinitrophenylhydrazone melted at $132.6-133^\circ$ (cor.) and mixed m. p. with the previous sample showed no depression. A neutralization equivalent was taken and gave a value of 326.

Since the 2,4-dinitrophenylhydrazone of 2-ketoheptonic acid was not known, the acid was prepared by the method of Wallach²³ and this derivative prepared from it and purified; m. p. 132.5° (cor.). Mixed m. p. with the two derivatives mentioned above showed no depression.

The semicarbazone was also prepared from each ozonized product and found to have a m. p. of $145-146^\circ$ (cor.) from the enyne obtained from the solid acetylene carbinol and $144-145^\circ$ (cor.) from the enyne obtained from the

(19) Marvel, Pinkney, Nesty and Wiley, *THIS JOURNAL*, **58**, 972 (1936).

(20) Wang and Hu, *J. Chinese Chem. Soc.*, **10**, 1 (1943).

(21) The preparation of this cyclohexanone from *m*-xylene and from 2-methylcyclohexanone will be described elsewhere.

(22) Strain, *J. Biol. Chem.*, **102**, 137 (1933).

(23) Wallach, *Ann.*, **329**, 376 (1903).

liquid acetylene carbinol. Mixed m. p. of the two showed no depression. Wallach²³ gives a m. p. of 144–145° for this derivative.

2,6,6-Trimethyl-1-ethynylcyclohexene-1.—This enyne was made by the dehydration of 2,6,6-trimethyl-1-ethynylcyclohexanol-1. The following dehydrating agents were tried usually at temperatures above the b. p. of the carbinol and in an atmosphere of nitrogen: fused potassium hydrogen sulfate, aluminum oxide on pumice, calcined ammonium alum on pumice, a 50–50 mixture of aluminum oxide–aluminum sulfate on pumice, thorium oxide on pumice, barium oxide, *p*-toluenesulfonic acid, molten succinic anhydride, succinic anhydride and sulfuric acid, succinic anhydride and glacial metaphosphoric acid, succinic anhydride in dibutyl phthalate, anhydrous oxalic acid, aluminum phosphate on pumice and anhydrous magnesium sulfate. Acidic dehydrating agents gave small amounts of the enyne while basic dehydrating agents gave mostly decomposition products. Of all the combinations tried, aluminum phosphate (20 g.) on pumice (30 g.) at 270–290° gave yields of 18–20% of the enyne per pass with only 50–60% of the carbinol recovered unchanged. When 22.6 g. of the acetylenecarbinol was added dropwise to a molten mixture of succinic anhydride (25 g.) and glacial metaphosphoric acid (0.4 g.) at 240–260° and under a slightly reduced nitrogen pressure (400 mm.), a product was obtained which when fractionated gave a fraction (6.7 g.) b. p. 60–80° (18 mm.). On the basis of its Zerewitinoff value, a yield of 26% of the enyne was obtained. However, on account of a large amount of tar formation, very little or no unchanged carbinol was recovered. When a similar dehydration was done in dibutyl phthalate (150 cc.) containing succinic anhydride (16 g.) under similar pressure and temperature conditions, yields of 12–15% of the enyne were obtained with slightly over 80% of the carbinol recovered unchanged. Similarly when 80 g. of the carbinol was heated with 61 g. of anhydrous oxalic acid¹⁸ at 170° under a slightly reduced pressure a product was obtained which when fractionated gave a fraction (26 g.) b. p. 75° (30 mm.). The Zerewitinoff value was only 0.3 corresponding to a yield of 10% of the enyne.

Since the silver derivative of this enyne precipitates instantly from an alcoholic ammoniacal silver nitrate solution, and the acetylene carbinol fails to give a precipitate even after one to two hours, the enyne was purified by this method as in the previous cases. The recovered pure enyne was found to boil at 56–57° (18 mm.) or 72–74° (30 mm.) and to give good analytical values; n_D^{25} 1.4745; d_4^{25} 0.8574; MR_D (calcd.) 48.33; MR_D (obsd.), 48.55.

Anal. Calcd. for $C_{11}H_{16}$: C, 89.11; H, 10.89; unsaturation, 3.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 89.20, 89.10; H, 10.82, 10.75; unsaturation, 3.28 (Pt); A. H. (Zerewitinoff), 0.90, 1.01.

Phenylacetylene.—This acetylene was prepared by the dehydrobromination of styrene dibromide (m. p. 74–75°) with sodamide in liquid ammonia.²⁴ A product was obtained which had a b. p. of 139.5–140.5° and an n_D^{25} 1.5459.

1-[Cyclohexan-1'-ol-yl]-3-methyl-3-hydroxy-4-chlorobut-1-ene-1.—Using the usual Grignard technique, 372 g. of 1-ethynylcyclohexanol-1 was converted to the corresponding magnesio salt acetylene Grignard by allowing it to react in 3 l. of anhydrous ether with ethylmagnesium bromide prepared from 146 g. of magnesium and 719 g. of ethyl bromide. The acetylene Grignard was then allowed to react with 277.5 g. of freshly distilled chloroacetone. The mixture was then hydrolyzed with an ice-ammonium chloride solution and the product obtained fractionated under a reduced pressure; b. p., 155–157° (4–5 mm.) or 115–116° (10⁻³ mm.); yield 400 g. (62%). When this was allowed to stand at 0° overnight, it solidified and was recrystallized from petroleum ether into colorless prisms; m. p., 58–60°.

Anal. Calcd. for $C_{11}H_{17}O_2Cl$: C, 60.95; H, 7.90; Cl, 16.32; unsaturation, 2.0 $\overline{\overline{}}$; A. H., 2.0. Found: C, 59.90, 60.13; H, 7.76, 7.38; Cl, 16.99, 17.16; unsaturation, 3.55 (Pt), 3.5 (Pd) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.88, 2.03.

1-[2',6',6'-Trimethylcyclohexan-1'-ol-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—A Grignard was prepared from 30 g. of magnesium and 138 g. of ethyl bromide in 1500 cc. of anhydrous ether. To this was added in the course of two hours 100 g. of 2,6,6-trimethyl-1-ethynylcyclohexanol-1. After the Grignard of the acetylene carbinol was formed, 55.7 g. of chloroacetone was added slowly at 0° then the mixture stirred overnight at room temperature. The mixture was then hydrolyzed with an ice-ammonium chloride solution and the product obtained fractionated; b. p. 65–67° (10⁻⁴ mm.). The highly viscous distillate (69 g.) was allowed to stand at 0° for three weeks whereby it solidified. This was recrystallized from petroleum ether into colorless needles; m. p., 41–42°.

Anal. Calcd. for $C_{14}H_{23}O_2Cl$: Cl, 13.72; unsaturation, 2.0 $\overline{\overline{}}$; A. H., 2.0. Found: Cl, 14.04, 14.13; unsaturation, 3.47 (Pt), 2.1 (Pd) $\overline{\overline{}}$; A. H. (Zerewitinoff), 2.24.

1-[Cyclohexan-1'-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—Ethylmagnesium bromide (0.5 mol) was made in 500 cc. of anhydrous ether and cooled in nitrogen with an ice-salt mixture. To this was added dropwise with stirring in the course of two hours 60 g. of 1-ethynylcyclohexene-1 (A. H., 0.9) in 200 cc. of ether. The mixture was stirred in nitrogen at room temperature for twenty-four hours, then cooled with an ice-salt mixture and to it added 47.2 g. of chloroacetone in 200 cc. of ether. The solution was stirred at room temperature for six hours then hydrolyzed with 200 cc. of cold saturated ammonium chloride solution. A product was obtained which when fractionated yielded 40 g. (40% yield) of a light orange colored liquid; b. p. 110–116° (4 mm.) or 60–63° (10⁻³ mm.); n_D^{25} 1.5259; d_4^{25} 1.1090; MR_D (calcd.), 54.72; MR_D (obsd.), 54.96.

Anal. Calcd. for $C_{11}H_{15}OCl$: C, 66.4; H, 7.56; Cl, 17.9; unsaturation, 3.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 66.15; H, 7.61; Cl, 18.2; unsaturation, 3.3 (Pt) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.0.

1-[2'-Methylcyclohexan-1'-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3.—Using a similar technique as in the previous case, a chlorohydrin was obtained in 54% yield from 2-methyl-1-ethynylcyclohexene-1 and chloroacetone. The product obtained had a b. p. of 115–130° (4 mm.) and gave good analytical results; n_D^{25} 1.5360; d_4^{25} 1.111; MR_D (calcd.), 59.34; MR_D (obsd.), 59.63. It also had an absorption band in the ultraviolet at 2270 Å., $\log \epsilon_{mol}$ 4.072.

Anal. Calcd. for $C_{12}H_{17}OCl$: C, 67.75; H, 8.06; Cl, 16.77; unsaturation, 3.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 67.98; H, 8.04; Cl, 16.81; unsaturation, 3.3 (Pt) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.0.

3-Methyl-1-phenyl-4-chloro-1-but-1-yn-ol-3.—In a similar manner a chlorohydrin was obtained in a yield of 52.5% from phenylacetylene and chloroacetone. This chlorohydrin was found to boil at 94–96° (1 mm.); n_D^{25} 1.5624.

Anal. Calcd. for $C_{11}H_{11}OCl$: C, 67.86; H, 5.70; Cl, 18.22. Found: C, 66.91; H, 5.92; Cl, 19.86.

The purification of this chlorohydrin was found to be more difficult than that of the others in view of the presence of small quantities of diphenyldiacetylene which was isolated and identified.²⁵

1-[Cyclohexan-1'-ol-yl]-3-methyl-3-epoxybutyne-1.—A solution of 181 g. of 1-[cyclohexan-1'-ol-yl]-3-methyl-4-chloro-1-but-1-yn-ol-3 in 500 cc. of dry ether was added dropwise in the course of two hours to a well-stirred suspension in nitrogen of 100 g. of freshly powdered potassium hydroxide in 750 cc. of ether. The mixture turned brick-red. Stirring was continued for two hours longer than the mixture treated with 500 cc. of cold water. A product

(24) Nieuwland, Vaughn and Vogt, *THIS JOURNAL*, **56**, 2121 (1931).

(25) Black, Ph.D. Thesis, M. I. T., July, 1947.

was isolated from the ethereal layer which was fractionated and the fraction (120 g.) boiling at 90–94° (10⁻³ mm.) collected. When allowed to stand at 0° overnight, this product solidified and was recrystallized from petroleum ether; m. p. 47–48°.

Anal. Calcd. for C₁₁H₁₆O₂: C, 73.33; H, 8.89; unsaturation, 2.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 73.03, 73.07; H, 8.89, 8.67; unsaturation, 4.4 (Pt), 3.9 (Pd) $\overline{\overline{}}$; A. H. (Zerewitinoff), 0.93.

This epoxide gave a positive test with the fuchsin aldehyde reagent and formed a 2,4-dinitrophenylhydrazone in dilute hydrochloric acid solution; m. p., 160–164°. It exhibited no band in the ultraviolet; only end absorption.

1-[2',6',6'-Trimethylcyclohexan-1'-ol-yl]-3-methyl-3-epoxybutyne-1.—This epoxide was made from the corresponding chlorohydrin by the usual dehydrochlorination technique using powdered potassium hydroxide. A product was obtained which was fractionated under a high vacuum; b. p. 55–58° (10⁻⁴ mm.). This product was induced to crystallize, then was recrystallized from petroleum ether; m. p., 81–82°.

Anal. Calcd. for C₁₄H₂₂O₂: C, 75.63; H, 9.97; unsaturation, 2.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 75.36, 75.62; H, 10.14, 10.17; unsaturation, 3.3 (Pt), 2.4 (Pd) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.04.

Although this epoxide gave a negative fuchsin-aldehyde test, it formed a 2,4-dinitrophenylhydrazone with Lund's reagent; m. p., 185–187°. This phenylhydrazone had an ultraviolet absorption spectrum (alcohol) with a well-defined maximum at 400 m μ , log ϵ_{mol} . 4.70. This epoxide also showed an end absorption.

1-[Cyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1.—Employing the usual technique this epoxide was prepared by the dehydrochlorination of the corresponding chlorohydrin with powdered potassium hydroxide or sodamide. Purification of this epoxide was rendered more difficult by its instability toward air oxidation, and frequently several fractionations were essential before a pure product was obtained. Physical constants and other analytical data had to be obtained immediately upon final fractionation. A yield of 33.5% of the pure epoxide was obtained; b. p. 64–64.5° (1 mm.); n_D^{25} 1.5145; d_4^{25} 0.9960; *MRD* (calcd.), 47.77; *MRD* (obsd.), 49.01. It showed a maximum in the ultraviolet at 232 m μ , log ϵ_{mol} . 4.32.

Anal. Calcd. for C₁₁H₁₄O: C, 81.44; H, 8.70; unsaturation, 3.0 $\overline{\overline{}}$. Found: C, 80.81; H, 8.63; unsaturation, 3.3 (Pt) $\overline{\overline{}}$.

This epoxide gave a positive test (slow) with the fuchsin-aldehyde reagent and formed an orange 2,4-dinitrophenylhydrazone with Lund's reagent (hot); m. p., 157–158° (cor.).

Anal. Calcd. for C₁₇H₁₈O₄N₄: C, 59.61; H, 5.30; N, 16.37. Found: C, 59.49; H, 5.99; N, 16.28.

Its absorption spectrum (alcohol) showed two well-defined maxima at 369 m μ (log ϵ_{mol} . 4.53) and 258 m μ (log ϵ_{mol} . 4.44), respectively.

1-[2'-Methylcyclohexen-1'-yl]-3-methyl-3-epoxybutyne-1.—Similarly this epoxide was prepared in 31% yield by the technique given above, and was found to have similar properties as the previous epoxide; b. p., 64–66° (1 mm.); n_D^{25} 1.5058; d_4^{25} 0.9942; *MRD* (calcd.), 52.39; *MRD* (obsd.), 52.70. It also showed a maximum in the ultraviolet at 232 m μ , log ϵ_{mol} . 4.19.

Anal. Calcd. for C₁₂H₁₆O: C, 81.76; H, 9.15; unsaturation, 3.0 $\overline{\overline{}}$. Found: C, 81.33; H, 9.24; unsaturation, 3.2 (Pt) $\overline{\overline{}}$.

This epoxide gave a positive test (slow) with the fuchsin-aldehyde reagent and formed an orange 2,4-dinitrophenylhydrazone; m. p., 158–159° (cor.).

Anal. Calcd. for C₁₉H₂₀O₄N₄: C, 60.66; H, 6.65. Found: C, 60.52; H, 6.34.

The absorption spectrum (alcohol) of this phenylhydrazone showed also two well-defined maxima at 377 m μ (log ϵ_{mol} . 4.35) and 260 m μ (log ϵ_{mol} . 4.38), respectively.

3-Methyl-1-phenyl-3-epoxybutyne-1.—This epoxide was also prepared by the usual technique in 43.5% yield (using powdered potassium hydroxide) or 40% yield (using sodamide). It boiled at 65–67° (1 mm.); n_D^{25} 1.5570; d_4^{25} 0.9968; *MRD* (calcd.), 46.84; *MRD* (obsd.), 51.02. It also showed a maximum in the ultraviolet at 243 m μ , log ϵ_{mol} . 4.29.

Anal. Calcd. for C₁₁H₁₆O: C, 83.50; H, 6.37; unsaturation, 5.0 $\overline{\overline{}}$. Found: C, 82.84; H, 6.42; unsaturation, 5.2 (Pt) $\overline{\overline{}}$.

A reddish-orange 2,4-dinitrophenylhydrazone was also prepared, m. p., 96–97° (cor.).

Anal. Calcd. for C₁₇H₁₈O₄N₄: C, 60.17; H, 4.46; N, 16.52. Found: C, 60.10; H, 4.34; N, 15.65.

1-[Cyclohexen-1'-yl]-3-methyl-1,5-hexadiyn-3-ol (VIII).—Using lithium acetylide (from 0.8 g. lithium in liquid ammonia (1.5 liters), 16.4 g. of 1-cyclohexen-1'-yl)-3-methyl-3-epoxybutyne-1 was converted into the crude carbinol (VIII). The product was fractionated from a pot molecular still and the fraction (7 g.) boiling at bath temperature 100° (10⁻⁴ mm.) collected and crystallized from petroleum ether; m. p. 63–67°. This product is rather unstable and after a few days it turns dark yellow. With alcoholic ammoniacal silver nitrate it gives a yellowish-white precipitate showing the presence of an acetylene group.

Anal. Calcd. for C₁₃H₁₆O: unsaturation, 5 $\overline{\overline{}}$; A. H., 2.0. Found: unsaturation, 4.76 $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.93.

3-Methyl-1-phenyl-1-hexyn-4-ol (IX).—A Grignard reagent was prepared from 3.2 g. of magnesium and 14.6 g. of ethyl bromide in 100 cc. of anhydrous ether. The solution was cooled to 0° and to it was added dropwise 17.5 g. of 3-methyl-1-phenyl-3-epoxybutyne-1 in 40 cc. of ether. The mixture was then stirred in nitrogen at room temperature for three hours then hydrolyzed at 0° with 8 g. of ammonium chloride in 50 cc. of water. A product was obtained which was fractionated and the fraction (12 g., 57.7% yield) boiling at 90–94° (1 mm.) collected and analyzed; n_D^{25} 1.5458; d_4^{25} 0.9865; *MRD* (calcd.), 58.16; *MRD* (obsd.), 60.34.

Anal. Calcd. for C₉H₁₄O: C, 82.93; H, 8.57; unsaturation, 5.0 $\overline{\overline{}}$. Found: C, 82.95; H, 8.55; unsaturation 5.0 (Pt) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.0.

3-Methyl-1-phenylhexanol-4.—Seven and a half grams of the foregoing unsaturated carbinol was partially hydrogenated in a mixture of 100 cc. of absolute ethanol and 2 cc. of glacial acetic acid using platinum oxide as catalyst. A product was obtained which was fractionated under a reduced pressure and the fraction (4.3 g., 54.7% yield) boiling at 90–92° (1 mm.) collected and analyzed; n_D^{25} 1.5020; d_4^{25} 0.9522; *MRD* (calcd.), 60.16; *MRD* (obsd.), 61.66.

Anal. Calcd. for C₁₃H₂₀O: C, 81.24; H, 10.49; unsaturation, 3.0 $\overline{\overline{}}$; A. H., 1.0. Found: C, 81.20; H, 10.82; unsaturation, 3.0 (Pt) $\overline{\overline{}}$; A. H. (Zerewitinoff), 1.0.

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Summary

- Several intermediates for the synthesis of vitamin A and vitamin A analogs have been synthesized and characterized.
- 1-[Cyclohexen-1'-yl]-3-methyl-3-epoxybu-

tyne-1 and related epoxides have been synthesized and their physical and chemical properties studied.

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Sterols. V. The *i*-Cholesterylamines

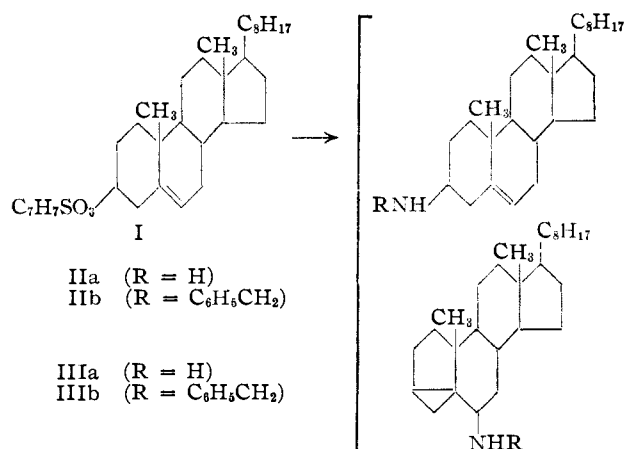
BY PERCY L. JULIAN, ARTHUR MAGNANI, EDWIN W. MEYER AND WAYNE COLE

In connection with transformations involving replacement reactions at the C₃ position of Δ^{5,6} unsaturated steroids, it was decided to explore carefully the possible role of *i*-steroids as intermediates in such conversions. The formation of an *i*-steroid has been shown to take place readily when the 3-*p*-toluenesulfonate of a Δ^{5,6}-steroid is treated with an appropriate reagent in the presence of a proton acceptor¹; however, in the absence of the latter a simple replacement seems to occur.

Our attempts to replace the 3-*p*-toluenesulfonate group by amino groups resulted in varying yields of 3-amino steroids, the relative basicity of the reagent employed strongly influencing the course of the reaction. It seemed logical to assume that we might be encountering the hitherto unknown *i*-steroid amines.

The unexpected ether solubility of the hydrochlorides of the *i*-steroid amines obscured at first their presence among the reaction products. Advantage was taken, however, of this property for their separation and characterization. This communication reports a study of certain *i*-cholesterylamines.

When cholesteryl *p*-toluenesulfonate (I) was



heated with ammonia at about 98°, there was obtained not only cholesterylamine (IIa)² but an iso-

(1) (a) Stoll, *Z. physiol. Chem.*, **207**, 147 (1932); (b) Beynon, Heilbron and Spring, *J. Chem. Soc.*, 907 (1936); (c) Wallis, Fernholz and Cephardt, *THIS JOURNAL*, **59**, 137 (1937).

(2) Windaus and Adaml, *Ber.*, **44**, 3051 (1911).

meric amine, *i*-cholesterylamine (IIIa), which was the predominant product. The separation of the isomeric cholesterylamines was greatly facilitated by the ether solubility of *i*-cholesterylamine hydrochloride. This hydrochloride, which melted at 212–214°, gave the crystalline *i*-cholesterylamine (IIIa), m. p. 77–79°. Both the *i*-amine and its hydrochloride were dextrorotatory, possessing specific rotations of +34° and +20°, respectively, in contrast to the negative rotation of cholesterylamine and its hydrochloride.

The reaction of cholesteryl *p*-toluenesulfonate (I) and benzylamine was found to proceed in an analogous fashion. Here again two isomeric amines were formed. The reaction mixture was separated into two fractions on the basis of the ether solubilities of the amine hydrochlorides. From the ether-insoluble hydrochloride, there was isolated benzylcholesterylamine (IIb), a levorotatory crystalline solid which melted at 115–117°. The purified ether-soluble hydrochloride which melted at 217–218° and possessed a specific rotation of –27° gave benzyl-*i*-cholesterylamine (IIIb), a viscous liquid which could not be crystallized. Unlike the hydrochloride, the free base was dextrorotatory, [α]_D + 12°.

In order to prove the constitution of benzylcholesterylamine, benzyl-*i*-cholesterylamine and *i*-cholesterylamine, these amines were degraded by alkaline decomposition of the respective chloroamines followed by acid hydrolysis.³ Upon treatment with an ethereal solution of hypochlorous acid, benzylcholesterylamine formed an N-chloro derivative which when decomposed with sodium ethoxide followed by acid hydrolysis gave cholesterylamine, identified as the acetyl derivative.² In a similar fashion benzyl-*i*-cholesterylamine was degraded. The product of this degradation, *i*-cholesterylamine, was identified as the crystalline hydrochloride. Further degradation of this hydrochloride via the N-chloro derivative gave a neutral product which, in spite of the inability to crystallize it, was *i*-cholestenone (IV), for upon treatment with hydrochloric acid in acetic acid in the known way,⁴ it readily yielded 3(β)-chlorocholestane-6-one. Thus the position

(3) Cf. Hellerman and Sanders, *THIS JOURNAL*, **49**, 1742 (1927).

(4) Ford, Chakravorty and Wallis, *ibid.*, **60**, 413 (1938).